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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/367,009	11/08/99	MORRIS	

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MORGAN, LEWIS & BOCKIUS
1800 M STREET NW
WASHINGTON DC 20036-5869

EXAMINER	
DAVIS,M	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

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Office Action Summary	Application No. 09/367,009	Applicant(s) Morris et al
	Examiner MINH TAM DAVIS	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 21, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above, claim(s) *12* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 1 sheet

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

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Applicant's election with traverse of group I claims 1-9, SEQ ID NO:3, in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the Examiner has not established that the groups of the restriction are patentably distinct, and that it would not be a burden for the Examiner to examine all the groups together. This is not found persuasive because of the reasons already set forth in the previous Office action, i.e. 1) different sequences are structurally distinct, 2) proteins are structurally distinct from nucleic acid molecules, and 3) diffent methods in groups I-III are different because they use different reagents protein markers, which are structurally distinct. Thus the searches for different groups are not co-extensive, and it would be a burden for the Examiner to search all the groups together.

However, after review and reconsideration, group IV, claims 10-11, drawn only to the extent of the protein of SEQ ID NO:3, and not SEQ ID NOs: 1 and 2, are rejoined with group I, because this application is a 371 of PCT/AU 98/00071.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-11, SEQ ID NO:3 are examined in the instant application.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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1. Claims 1-2, 5-6 are indefinite because claim 1 lacks a step correlating back to the preamble of claim 1.

2. Claims 3-4, 7-9 are indefinite, because in claim 3, it is not clear whether the presence of SEQ ID NO:3 is an indicator of a disease state, or the absence of SEQ ID NO:3 is an indicator of a disease state.

REJECTION UNDER 35 USC 101, UTILITY

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-11 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claims 1-11 are drawn to SEQ ID NO:3 or fragment thereof, and a method for detecting a disease, or breast or prostate cancer, comprising detecting the presence of SEQ ID NO:3 in tear samples, wherein the presence of SEQ ID NO:3 is an indication of a disease state.

The disclosed utilities for SEQ ID NO:3 or fragments thereof include detection of non-ocular diseases, or breast or prostate cancer, comprising detecting the presence of SEQ ID NO:3 in tear samples, wherein the presence of SEQ ID NO:3 is an indication of a disease state. However, neither the specification nor any art of record teaches what SEQ

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ID NO:3 is, what it does do. They do not teach a utility for any of the fragments claimed. They do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases.The asserted utility of SEQ ID NO:3 or spot 9 on gel electrophoresis is based on the assertion that SEQ ID NO:3 has structural homology to uteroglobins and rat prostatic steroid-binding protein C3, wherein uteroglobins and rat prostatic steroid-binding protein C3 are putative markers for breast and prostate cancer, respectively (specification, p.6).It is noted that none of the tear donors are disclosed to have cancer. Based on sequence similarity search, SEQ ID NO:3 is 98.6% similar to a fragment of uteroglobins, and is 36.6% similar to rat prostatic steroid-binding protein C3 (MPSRCH sequence similarity search, us-09-367-009.rsp, pages 1-3). However, it is clear that, although there is a 98.6%, and 36.6% identity between SEQ ID NO:3 and uteroglobins and rat prostatic steroid-binding protein C3, respectively, there is a 1.4% and 63.4% dissimilarity between SEQ ID NO:3 and uteroglobins and rat prostatic steroid-binding protein C3, respectively, and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative

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substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with a 1.4% and 63.4% dissimilarity between SEQ ID NO:3 and uteroglobins and rat prostatic steroid-binding protein C3, respectively, the function of the SEQ ID NO:3 polypeptide could not be predicted, based on sequence similarity with uteroglobins and rat prostatic steroid-binding protein C3, nor would it be expected to be the same as that of uteroglobins and rat prostatic steroid-binding protein C3. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational

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modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the errror rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrogngly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the

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unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 1.4% and 63.4% dissimilarity between SEQ ID NO:3 and uteroglobins and rat prostatic steroid-binding protein C3, respectively, the function of the SEQ ID NO:3 polypeptide could not be predicted, based on sequence similarity with uteroglobins and rat prostatic steroid-binding protein C3, nor would it be expected to be the same as that of uteroglobins and rat prostatic steroid-binding protein C3. Further, even if the polypeptide of SEQ ID NO:3 is a-uteroglobins or rat prostatic steroid-binding protein C3 like protein, neither the specification nor any art of record teaches what the polypeptide is, what it does. They do not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide, and the method of detection. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

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REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

If Applicant could overcome the above 101 and 112, first paragraph rejections, claims 1-9, 11 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:3 and a method for detecting breast or prostate cancer comprising detecting the presence of SEQ ID NO:3 in tear samples, does not reasonably provide enablement for "part" of SEQ ID NO:3 and a method for detecting "non-ocular diseases, any cancer, or genetic disorder" comprising detecting the presence of "part" of SEQ ID NO:3 in tear samples. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-9, 11 are drawn to part of SEQ ID NO:3 and a method for detecting "non-ocular diseases, cancer, or genetic disorder" comprising detecting the presence of part of SEQ ID NO:3 in tear samples.

It is noted that "part" of a polypeptide could be as little as one or two amino acids.

The specification discloses a polypeptide of SEQ ID NO:3. Due to the language "part", the claims read on a peptide, wherein the peptide is of any size, including a two amino acid sequence. It is unpredictable that a sequence of as little as one or two amino acids could be used as a marker for detecting cancer, because it is well known in the art that said probe would not be specific for the claimed SEQ ID NO:3. The specification does not teach how to use a peptide, wherein the peptide is of any size, including a one or two amino acid sequence, as a marker for detection of cancer. In the absence of a teaching of a method of how to use a peptide, wherein the peptide is of any size, including a one or two amino acid sequence, for detection of cancer, undue experimentation would be required to practice the claimed invention as broadly as claimed.

Further, the specification discloses that the invention relates to diagnosis of diseases in human by detecting a biomarker in tears, i.e. SEQ ID NO:3, wherein said

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diseases include cancer and genetic disorders, breast cancer and prostate cancer (p.1,2). The specification further discloses that SEQ ID NO:3 has structural homology to uteroglobins and rat prostatic steroid-binding protein C3, wherein uteroglobins and rat prostatic steroid-binding protein C3 are putative markers for breast and prostate cancer, respectively (specification, p.6).It is noted that none of the tear donors are disclosed to have cancer.

One cannot extrapolate the teaching in the specification to the claims because neither the art of record, nor the specification has identified non-ocular diseases, any cancer or any genetic disorder associated with SEQ ID NO:3, nor teaches how to discover non-ocular diseases using SEQ ID NO:3. Since there is no correlation between SEQ ID NO:3 and non-ocular diseases, or any cancer or any genetic disorder, it is unpredictable that SEQ ID NO:3 could be used as a marker for detecting non-ocular diseases, any cancer or any genetic disorder. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to SEQ ID NO:3 for detection of non-ocular diseases or cancer or genetic disorders. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence. Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. Clearly, there is no validation of the use of the claimed SEQ ID NO:3 as a biomarker for deteting any non-ocular disease, any cancer, or any genetic disorder.

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Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, *In re Fisher*, 166 USPQ 19 24 (CCPA 1970), and it cannot be predicted from the disclosure how to use the claimed polypeptide to detect non-ocular diseases, any cancer or any genetic disorder. Therefore, undue experimentation would be required to enable the claims as written.

REJECTION UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by US 6,066724.

Claim 1 is drawn to a fragment of SEQ ID NO:3.

It is noted that a fragment of a sequence could be as little as one or two amino acids.

US 6,066724 teaches a sequence which is 98.6% similar to SEQ ID NO:3, from amino acid 1 to 73 (MPSRCH sequence similarity search report, us-09-367-009-3.rai, page 1-2).

The reference does not specifically teach that the sequence is detectable in tears. However, the claimed sequence appears to be the same as the prior art sequence. The office does not have the facilities and resources to provide the factual evidence needed in

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order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of thisplication or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

August 31, 2001

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

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